Non-technical Abstract

A Phase II Trial of Vaccination with Autologous, Lethally Irradiated Melanoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Granulocyte-Macrophage Colony Stimulating Factor in Stage III and IV Metastatic Melanoma Patients

This clinical trial for patients with metastatic melanoma will investigate the use as therapeutic vaccines of autologous (from the patient), irradiated melanoma cells engineered by adenoviral mediated gene transfer to secrete human granulocyte-macrophage colony stimulating factor (GM-CSF). A total of up to 70 evaluable patients will be immunized with varying doses of engineered autologous melanoma cells weekly times three and then every two weeks until the supply is exhausted.

Extensive pre-clinical studies in murine tumor models demonstrated that this vaccination scheme stimulated potent, specific, and long-lasting tumor immunity. Based upon these findings, we initially conducted a Phase I clinical trial of this vaccination strategy in patients with metastatic melanoma. This study established the safety and biologic activity of this immunization scheme. However, this first trial involved the use of retroviral vectors to manufacture patient-specific vaccines. This complicated method presented a significant impediment to more detailed clinical investigation. We thus conducted a second Phase I trial employing adenoviral mediated gene transfer; this simplified method of vaccine production proved feasible, safe and immunogenic. We now propose a Phase II study aimed at extending these clinical findings in two important ways.

First, we will evaluate the feasibility, safety, and toxicity of this vaccination strategy in earlier stage melanoma patients. These investigations will yield new information regarding the doses of vaccines that can be manufactured in the context of regional disease as compared to the previous studies in disseminated disease. Moreover, the generation of host responses in earlier stage patients (who also likely received less prior therapy than more advanced patients) may differ from the previous studies; thus, we will analyze both toxicity and immunity in this patient cohort. If this trial reveals significant biologic activity without substantive toxicity, then these results would provide a foundation for undertaking a subsequent Phase III study testing the therapeutic efficacy of vaccination in the adjuvant setting.

Second, we will more thoroughly evaluate the biologic activity of this vaccination scheme in stage IV (the most advanced) melanoma patients. The prolonged survival (at least 44 months) of 10 of 35 subjects in the previous Phase I trial is intriguing, in view of the mean survival of only 6-9 months for patients with metastatic disease. Thus, we propose to determine in a larger cohort of advanced patients the two-year survival associated with vaccination. Lastly, blood and tumor samples obtained during the

course of immunization function as critical reagents for detailed analysis of vaccine-induced immune responses.